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(57) Abstract

The present invention relates to the use of compounds which interact with 5-HT1A receptors, especially azapirones or pharmaceutically acceptable salts thereof, for the preparation of medicaments for use in the treatment or prophylaxis of incontinence disorders, methods of treatment using these compounds and pharmaceutical compositions containing these compounds.

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MEDICAMENT FOR TREATMENT OR PROPHYLAXIS OF INCONTINENCE

The present invention relates to the treatment of incontinence disorders, and in particular to a new medical use for azapirones, and other compounds which interact with 5-HT1A receptors, in the treatment of urinary and fecal incontinence and related conditions.

The condition of incontinence is typified by the inappropriate flow of fluids in passages and from natural orifices of the body and includes both the flow of material from the body, for example in urinary and fecal inconvenience, and the retention of material in the body, for example in urinary retention.

Urinary incontinence may occur as the result of a number of medical conditions including the failure of voluntary control of vesical and urethral sphincters with constant or frequent involuntary passage of urine. Urinary incontinence conditions include active incontinence, intermittent incontinence, overflow incontinence, paradoxical incontinence, paralytic incontinence, stress incontinence and passive incontinence.

Treatment of urinary incontinence is in essence dependent on its type and severity. Generally speaking, there are three approaches, namely the use of pharmacologic agents, electrical stimulation, or surgery, the latter two being directed almost exclusively to the treatment of sphincters of the urogenital tract.

The pharmocological approach is directed primarily to increasing the capacity of incontinent patients to store urine. Pharmacologic drugs in use include those directed towards improving stability of the detrusor muscle in the bladder wall (and thus bladder capacity) by blocking cholinergic transmission and those having a

direct inhibitory effect on the smooth muscle of the bladder wall. Examples include anticholinergics (which suppress urgency and urgency incontinence as well as being useful in the treatment of neurogenic incontinence) such as belladonna, propantheline bromide, methantheline bromide, baclophene, prazocine and terodiline and the antimuscarinic agents oxybutynin, flavoxate hydrochloride and the antidepressant imipramine hydrochloride. The side-effects for all anticholinergics include dry mouth, visual blurring and decreased gastrointestinal motility with resulting constipation.

Urethral resistance may be improved by alpha agonists. Examples include phenylpropanolamine, ephedrine, and imipramine. Parasymphathomimetics (e.g. Urecholine) have been used with limited success in improving detrusor function. Most clinicians find, however, that significant improvement in bladder contractility requires such high doses of Urecholine that the side effects (gastrointestinal disturbance) become prohibitive.

The sympathetic nervous system exercises important control over the bladder and urethra. Since the bladder neck and proximal urethra contain mainly alpha-adrenergic receptors, alpha-adrenergic stimulation of the smooth muscle in these areas increases urethral resistance. Sympathomimetic agents that stimulate alpha-adrenergic receptors have been used to treat stress urinary incontinence (SUI) and include ephedrine, pseudoephedrine hydrochloride and phenylpropanolamine hydrochloride. Although these agents may be useful in patients with mild SUI, surgical correction is often preferable to chronic medication with its associated side-effects such as increased irritability, cardiac palpitations, anxiety and drowsiness. Moreover, none of these drugs cure severe SUI. Nerve stimulation may be used as an alternative treatment. Finally the operative

approach may be employed.

As with urinary incontinence, fecal incontinence may result from failure of voluntary control of rectal sphincters with involuntary passage of feces and flatus which may be due to anatomic disruption of the sphincters resulting from previous surgery, obstetric trauma, or other injuries. Neurologic problems are primary in other patients with anatomically intact sphincters. Procidentia is often associated with incontinence if it remains untreated for long periods. In patients whose sphincters are anatomically intact, operant conditioning is used to overcome incontinence. Various operations have been proposed for improving the function of intact sphincters, but the results are mixed. Elderly patients generally are prone to failure of the repair or prompt recurrence of incontinence.

Incontinence is a distressing condition which may severely incapacitate or stigmatize the sufferer. As can be seen from the above, present treatments are not entirely satisfactory since they may either not be effective on all types of incontinence, or they may involve invasive or unpleasant procedures such as surgery or nerve stimulation. Clearly, any new treatment which helps to relieve or improve symptoms in such patients in a simple and non-invasive manner would be of benefit.

Surprisingly, it has now been found that the azapirone class of psychotropic drugs compounds is particularly effective in relieving the symptoms of urinary and fecal incontinence and, accordingly are of benefit in the treatment or prophylaxis of urinary and fecal incontinence and other related disorders.

Thus, according to one aspect, the present invention provides the use of an azapirone or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or prophylaxis of incontinence disorders.

Azapirones are a novel class of drugs, known primarily for their neurological properties and demonstrate dopaminergic, noradrenergic and serotonin (5-hydroxy-tryptamine, 5-HT)-modulating effects without untoward side effects (see for example "Symposium on azapirones: a novel class of broad spectrum psychotropic agents 9.12.1989, USA; J. Clin. Psychopharm. 1990, 10(3) suppl.) Their primary use has been in the treatment of anxiety and depression, but more recently other uses have been proposed, for example in the treatment of sexual dysfunction (US-A-4,640,921), alcoholism (EP-A-0303951), motion sickness and chemically-induced emesis (US-A-4,943,428), cognitive disorders (WO 93/04681) and drug abuse (EP-A-0356997).

Generally speaking, azapirones may be defined as a class of compounds containing a 1,3-bisoxacyclo-2-azaalkane ring optionally containing other ring heteroatoms eg. sulphur.

The most notable members of the class include buspirone, ipsapirone, gepirone and tandospirone, although a range of other azapirone compounds and derivatives have also been described (see for example EP-A-0356997, EP-A-0442424, EP-A-303951, EP-A-455510, US-A-4,818,756, EP-A-0129128 and EP-A-082402). All such compounds and derivatives are included within the scope of this invention, as are all their pharmaceutically acceptable salts, including both organic and inorganic salts (eg. with alkali and alkaline earth metal, ammonium, ethanolamine, diethanolamine and meglumine, chloride, hydrogen carbonate, phosphate, sulphate and acetate counterions). Appropriate pharmaceutically acceptable salts are well described in the pharmaceutical literature. In addition, some of these salts may form solvates with water or organic solvents such as ethanol. Such solvates are also included within the scope of this invention.

Azapirones are partial agonists at 5-HT1A

receptors. Over the last few years it has become apparent that the ligand for these receptors, namely serotonin (5-HT) is associated directly or indirectly with a number of physiological phenomena, including appetite, memory, thermoregulation, sleep, sexual behaviour, anxiety, depression, and hallucinogenic behaviour (see Glennon, J. Med. Chem. 30, 1 (1987)).

5-HT receptors have been identified in the central nervous system (CNS; brain and spinal cord) and in peripheral tissues including the gastrointestinal tract, lung, heart, blood vessels, and various other smooth muscle tissues. Multiple types of 5-HT receptors have been recognized. These receptors have been classified as 5-HT1, 5-HT2, and 5-HT3 with at least the 5-HT1 receptor being further divided into sub-classes 5-HT1A, 5-HT1B, 5-HT1C, and 5-HT1D.

The primary focus of research efforts surrounding the biochemistry and physiology of serotonin and serotonin agonists has been directed toward the CNS, and in particular to the brain. It has also been identified that 5-HT receptors in smooth muscle of the gastrointestinal tract mediate contraction of this tissue. In EP-455510 it has been disclosed that 5-HT1A agonists inhibit the secretion of gastric acid.

While not wishing to be limited by theory, it appears that the therapeutic effect on incontinence disorders may involve the activity of azapirones directly on 5-HT1A receptors of the target organs, or possibly the small number of 5-HT1A receptors found in nerve fibres connecting these organs to the autonomic nerve system.

Viewed from a further aspect therefore, the present invention can be seen to provide use of a compound which interacts with 5-HT1A receptors, or a pharmaceutically acceptable salt thereof for the preparation of a medicament for use in the treatment or prophylaxis of incontinence disorders.

Compounds interacting with 5-HT1A receptors which may be used according to the invention include agonists, partial agonists and antagonists. Receptor agonists are defined as those compounds capable of binding to the receptor and directly activating its activity. Receptor antagonists bind to the receptor and block or inhibit its biological activity. Partial agonists both up-regulate and down-regulate the receptor and may exhibit both pre-synaptic and post-synaptic effects. Generally speaking, partial agonists directly activate the receptor, but produce a smaller maximal effect. A wide range of such compounds are well known and widely described in the literature.

Procedures for performing binding assays to determine 5-HT1A agonist activity are known to those skilled in the art and include, for example, the techniques described in Wong et al., Life Sciences, 46, 231-235 (1990) and the references cited therein. The relationship between apparent binding affinity (K_1) as a function of inhibitor IC_{50} values, radioligand concentration and dissociation of the ligand-receptor complex is also known to those skilled in the art. For example, see Cheng et al., Biochemical Pharmacology, 22, 3099-3108 (1973); and Taylor et al., Life Sciences, 41, 1961-1969 (1987). Likewise 5-HT1A antagonist activity may also be easily determined and assayed (see for example J. Pharmacol. Exp. Ther. 238, 248-253 (1986) and J. Pharmacol. Exp. Ther. 258, 58-65 (1991).

In addition to the azapirones, 5-HT1A agonists and partial agonists include the following classes of compounds which may be used according to the present invention:

1) 2-amino-1,2,3,3,4-tetrahydronaphthalenes and 3-amino chromanes;
2) 4-amino-1,3,4,5-tetrahydrobenz-[c,d]indoles;
3) non-endogenous indoles;

4) aryloxy propanolamines;
5) benzodioxanes;
6) phenylcyclopropylamines;
7) piperidinylmethyl tetrahydroisoquinolines; and
8) N-arylpiperazines (including, inter alia, those which are azapirones).

Such compounds are described in more detail in EP-A-0455510 and the references cited therein.

WO93/04681 describes a range of suitable partial agonists and antagonists, which, in addition to the azapirones, include:

1) piperazine derivatives such as 1-[10,11-dihydro-8-(methylthio)-dibenzo[b,f]thiepin-10-yl]-4-methylpiperazine (Methiothepin);
2) 1,1-diethyl-3-(8a-ergolinyl) urea derivatives such as Lisuride (die Vivo and Maayani, J. Pharmacol, Exp. Ther. 238, 248-253) und Terguride (for example Kehr, Eur. J. Pharmacol. 97, 111-119 (1984));
3) 2-amino-tetralines such as 5-fluoro-8-hydroxy-2-(dipropylamino)-tetraline (J. Med. Chem. 33, 1541-1544 (1990)) and Spiperon (8-[3-(p-fluobenzoyl)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one).

As mentioned above, pharmaceutically acceptable salts and solvates of such compounds may readily be prepared using counterions and techniques well known in the art. All such salts and solvates as well as any isomers (eg. stereoisomers and/or enantiomers) and their mixtures are all included according to the invention.

Incontinence disorders which may be treated according to the present invention, include all those in which inappropriate flux of fluid occurs in passages or from natural orifices of the animal body. Typically, incontinence disorders may be associated with conditions

of the gastrointestinal and urogenital tracts which include for example urinary and fecal incontinence and urinary retention.

Other aspects of the invention accordingly provide a method of treatment of the human or non-human animal body to combat incontinence disorders, said method comprising administering to said body a compound interacting with 5-HT1A receptors, or a pharmaceutically acceptable salt thereof.

More particularly, the invention provides a method of treatment of the human or non-human animal body to combat incontinence disorders, said method comprising administering to said body an azapirone or a pharmaceutically acceptable salt thereof.

As used herein, the term "combat" includes both therapy and prophylaxis, in particular of individuals with a history of, or at risk from, incontinence disorders.

The compounds useful in practising the invention are preferably formulated prior to administration. The present invention therefore also provides a pharmaceutical composition for use in the treatment or prophylaxis of incontinence disorders, said composition comprising a compound interacting with 5-HT1A receptors or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, diluent or excipient.

In one preferred embodiment, such compositions may comprise an azapirone or a pharmaceutically acceptable salt thereof.

The active ingredient in such compositions may comprise from about 0.1% to about 99% by weight of the formulation. By "pharmaceutically acceptable" is meant that the ingredient must be compatible with other ingredients of the compositions as well as physiologically acceptable to the recipient.

Pharmaceutical compositions for use according to

the present invention may be formulated in conventional manner using readily available ingredients, for example as described in any of the afore-mentioned patent specifications. Thus, the active ingredient may be incorporated, optionally together with other active substances, with one or more conventional carriers, diluents and/or excipients, to produce conventional galenic preparations such as tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments, soft and hard gelatin capsules, suppositories, sterile injectable solutions sterile packaged powders, and the like.

Examples of suitable carriers, excipients, and diluents are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, aglinates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, water, water/ethanol, water/ glycol, water/polyethylene, glycol, propylene glycol, methyl cellulose, methylhydroxybenzoates, propyl hydroxybenzoates, talc, magnesium stearate, mineral oil or fatty substances such as hard fat or suitable mixtures thereof. The compositions may additionally include lubricating agents, wetting agents, emulsifying agents, suspending agents, preserving agents, sweetening agents, flavouring agents, and the like. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, eg. with each dosage containing from about 0.1 to about 500 mg of the active ingredient.

The precise dosage of the active compound to be administered and the length of the cause of treatment will, of course, depend on a number of factors including

for example, the age and weight of the patient, the specific condition requiring treatment and its severity, and the route of administration. Generally however, an effective dose may lie in the range of from about 0.01 mg/kg to about 20 mg/kg per day, eg from about 0.05 to about 10 mg/kg per day, preferably from about 0.2 to 1.0 mg/kg per day, administered one or more times per day. Thus for example, an appropriate daily dose for an adult, may be from 10 to 100 mg per day, eg 20 to 50 mg per day.

The administration may be by any suitable method known in the medicinal arts, including for example oral, parenteral (eg. intramuscular, subcutaneous, intraperitoneal or intravenous) rectal or topical administration or administration by inhalation.

The invention will now be described in more detail by way of the following non-limiting Examples:

Formulation Example 1 - Hard gelatin capsules

Capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
starch, dried	200
magnesium stearate	10
Total	460 mg

The active ingredient is selected from those shown in Table 1. The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation Example 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Active ingredient	250
cellulose, microcrystalline	400
silicon dioxide, fumed	10
stearate acid	5
Total	665 mg

The active ingredient is selected from those shown in Table 1. The components are blended and compressed to form tablets each weighing 665 mg.

Formulation Example 3

	Weight %
Active ingredient	0.25
ethanol	29.75
Propellant 22 (chlorodifluoromethane)	70.00
Total	100.00

The active compounds, selected from Table 1, is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation Example 4

Tablets, each containing 60 mg of active ingredient, are made as follows:

Active ingredient	60 mg
starch	45 mg
microcrystalline cellulose	35 mg
polyvinylpyrrolidone (as 10% solution in water)	4 mg
sodium carboxymethyl starch	4.5 mg
magnesium stearate	0.5 mg
talc	1 mg
Total	150 mg

The active ingredient (selected from Table 1), starch and cellulose are sieved and mixed thoroughly. The aqueous solution containing polyvinyl pyrrolidone is mixed with the resultant powder, and the mixture then is

passed again through a sieve. The granules so produced are dried at 50°C and passed through a sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation Example 5

Suspensions, each containing 50 mg of active ingredient per ml dose, are made as follows:

Active ingredient	50 mg
sodium carboxymethyl cellulose	50 mg
syrup	1.25 ml
benzoic acid solution	0.10 ml
flavour	q.v.
colour	q.v.
purified water to total	5 ml

The active ingredient (selected from Table 1), passed through a sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavour and colour are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Example 6

One female patient suffering from both fecal and urinary incontinence reported relief of the symptoms after treatment with buspirone.

The patient's fecal incontinence started immediately

after a delivery in 1987, after which the patient no longer felt the urge to defecate. Two years later the urinary incontinence started. The fecal incontinence was diagnosed as the result of a sensory nerve damage at the Department of neurology at the National hospital. The etiology of the urinary incontinence has not been found.

As a result of buspirone (Buspar) treatment of 40 mg per day, the patient's urinary incontinence improved immediately. The patient's fecal incontinence improved after a period of 3-4 weeks, with a return of the patient's urge to defecate.

Example 7

One 40 year old, female patient suffering from migraine and bladder incontinence for many years, subjected to surgical intervention three times (stoma), and also suffering from an anxiety disorder, reported relief of these symptoms after treatment with buspirone.

As a result of buspirone treatment of 25 mg a day from 4th August 1992, the patient's anxiety was markedly improved. After 2-3 weeks, the following additive effects were noted:

- The frequency of the patient's migraine attacks reduced (2 attacks during the last 4 months in comparison to approximately twice monthly prior to medication).

- The patient's urinary incontinence, persistent since 1975, disappeared.

After 2 months treatment with buspirone was stopped,

whereafter the symptoms gradually relapsed. After 1 month the patient was once again treated with buspirone resulting in the same excellent effects.

Example 8

The patient is a 35 year old woman. In 1988 she was operated on for a prolaps of L5 in the columna. At the time of surgery she had urinary retention. Since then she has suffered continuously from low back pain, and irridiation pain from the L5/S1 area. She has been using a back cast, but with only temporary relief of her symptoms. A further operation is now being considered.

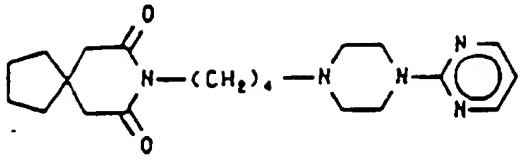
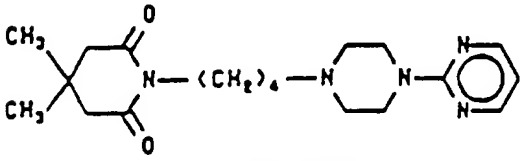
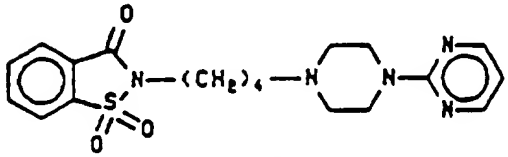
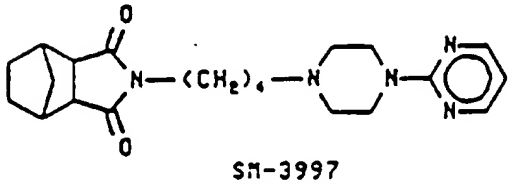
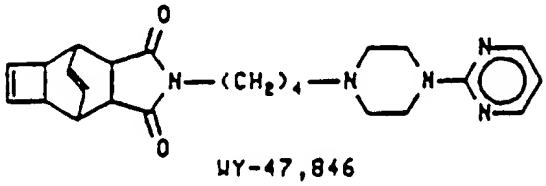
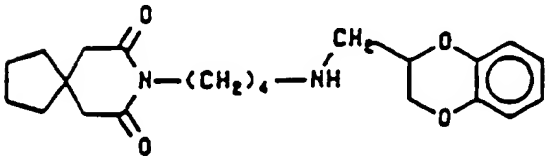
Since 1988 she has also had long periods with urinary problems. On occasion she has been incontinent, but mostly has suffered from urinary retention. She has been taught self-catherisation, and uses this when necessary. As a part of this routine she also measures her residual urine.

During a period in which the patient was experiencing urinary retention she was given buspirone at a dose of 30 mg a day. After two weeks of treatment she reported a reduction of residual urine, and soon no longer needed catherisation. Buspirone was administered for a total period of 4 months, without relapse of the patient's urinary symptoms.

About 6 months after the end of the 4 months buspirone administration period, she once again developed urinary retention and hence started self-catherisation. On administration of buspirone at the same dose as used previously, the patient once again experienced the same significant relief of her symptoms.

Table 1

Specific Azapirone Compounds

STRUCTURE	REFERENCE
 BUSPIRONE	US 3,717,634
 GEPIRONE	US 4,423,049
 IPSAPIRONE	EP 129,128A
 SM-3997	US 4,507,303
 WY-47,846	J.Med.Chem., 1988 31, 1382-1392
 MDL 72832	US 4,612,312

Claims

1. The use of a compound which interacts with 5-HT1A receptors, or a pharmaceutically acceptable salt thereof for the preparation of a medicament for use in the treatment or prophylaxis of incontinence disorders.

2. The use as claimed in claim 1 wherein the compound is a 5-HT1A agonist, partial agonist or antagonist.

3. The use as claimed in claim 1 or 2 wherein the compound is selected from the list:

1) 2-amino-1,2,3,3,4-tetrahydronaphthalenes and 3-amino chromanes;
2) 4-amino-1,3,4,5-tetrahydrobenz-[c,d]indoles;
3) non-endogenous indoles;
4) aryloxy propanolamines;
5) benzodioxanes;
6) phenylcyclopropylamines;
7) piperidinylmethyl tetrahydroisoquinolines;
8) N-arylpiperazines;
9) piperazine derivatives;
10) 1,1-diethyl-3-(8a-ergolinyl) urea derivatives; and
11) 2-amino-tetralines.

4. The use as claimed in any one of claims 1 to 3 wherein the compound is an azapirone, derivative or pharmaceutically acceptable salt thereof.

5. The use as claimed in claim 4 wherein the azapirone is buspirone or a pharmaceutically acceptable salt thereof.

6. The use as claimed in any one of claims 1 to 5 wherein the incontinence disorders are associated with conditions of the gastrointestinal or urogenital tracts.

7. The use as claimed in claim 6 wherein the incontinence disorder is urinary incontinence, fecal incontinence or urinary retention.

8. The use as claimed in any one of claims 1 to 7 wherein the medicament contains the compound in an amount sufficient to administer an effective dose from about 0.1mg/kg to about 20mg/kg.

9. The use as claimed in claim 8 wherein the effective dose is from about 0.05 to 10mg/kg.

10. A method of treatment of the human or non-human animal body to combat incontinence disorders, said method comprising administering to said body a compound interacting with 5-HT1A receptors, or a pharmaceutically acceptable salt thereof.

11. A method as claimed in claim 10 wherein the compound is a 5-HT1A agonist, partial agonist or antagonist.

12. A method as claimed in claim 10 or 11 wherein the compound is selected from the list:

1) 2-amino-1,2,3,3,4-tetrahydronaphthalenes and 3-amino chromanes;
2) 4-amino-1,3,4,5-tetrahydrobenz-[c,d]indoles;
3) non-endogenous indoles;
4) aryloxy propanolamines;
5) benzodioxanes;
6) phenylcyclopropylamines;
7) piperidinylmethyl tetrahydroisoquinolines;
8) N-arylpiperazines;
9) piperazine derivatives;
10) 1,1-diethyl-3-(8a-ergolinyl) urea derivatives; and
11) 2-amino-tetralines.

13. A method as claimed in any one of claims 10 to 12 wherein the compound is an azapirone, derivative or pharmaceutically acceptable salt thereof.

14. A method as claimed in claim 13 wherein the azapirone is buspirone or a pharmaceutically acceptable salt thereof.

15. A method as claimed in any one of claims 10 to 14 wherein the incontinence disorders are associated with conditions of the gastrointestinal or urogenital tracts.

16. A method as claimed in claim 15 wherein the incontinence disorder is urinary incontinence, fecal incontinence or urinary retention.

17. A method as claimed in any one of claims 10 to 16 wherein said compound is administered at a dose of from about 0.1mg/kg to about 20mg/kg.

18. A method as claimed in claim 17 wherein the dose is from about 0.05 to 10mg/kg.

19. A pharmaceutical composition for use in the treatment or prophylaxis of incontinence disorders, said composition comprising a compound interacting with 5-HT1A receptors or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 5, together with at least one pharmaceutically acceptable carrier, diluent or excipient.

20. A pharmaceutical composition as claimed in claim 19 wherein the incontinence disorders are associated with conditions of the gastrointestinal or urogenital tracts.

21. A pharmaceutical composition as claimed in claim 20 wherein the incontinence disorder is urinary

incontinence, fecal incontinence or urinary retention.

22. A pharmaceutical composition as claimed in any one of claims 19 to 21 wherein the composition contains the compound in an amount sufficient to administer an effective dose from about 0.1mg/kg to about 20mg/kg.

23. A pharmaceutical composition as claimed in claim 22 wherein the effective dose is from about 0.05 to 10mg/kg.

INTERNATIONAL SEARCH REPORT

I tional Application No
PCT/GB 95/01995

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 558 245 (RECORDATI S.A.CHEMICAL AND PHARMACEUTICAL COMPANY) 1 September 1993 see page 6, column 11 - column 31 ---	1-23
X	J.PHARMACOL.EXP.THER., vol. 262, no. 1, July 1992 pages 181-189, A.LECCI ET AL. 'Involvement of 5-Hydroxytryptamine 1A Receptors in the Modulation of Micturition Reflexes in the Anesthetized Rat' see the whole document --- -/--	1-23

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 November 1995	20.12.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Theuns, H

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/01995

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.AM.VET.MED.ASSOC., vol. 203, no. 2, 15 July 1993 pages 254-258, B.L.HART ET AL. 'Effectiveness of buspirone on urine spraying and inappropiate urination in cats' see the whole document -----	1-23

INTERNATIONAL SEARCH REPORT

.nternational application No.
PCT/GB95/01995

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
PLEASE SEE ATTACHED SHEET!

2. [X] Claims Nos.: 1-4; 6-23
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
PLEASE SEE ATTACHED SHEET!

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION C NTINUED FROM PCT/ISA/210

INCOMPLETE SEARCH

Remark:

Although claims 10-18 are directed to a method of treatment of the human/animal body the search has been based on the alleged effects of the compound/composition.

The definition of a compound by means of its ability to interact with 5-HT1A receptors is not a proper definition of a chemical compound. A complete search consequently is virtually impossible for such subject matters.

The definition of compounds by indicating merely a structural skeleton or a structural class is not a proper definition of a chemical compound. A complete search consequently is virtually impossible for such subject matters.

The further definition of such a compound by the term "non-endogenous" is not a proper limitation defining such compounds in structural terms. As a consequence, a complete search is virtually impossible for such subject matters.

In view of the large number of compounds which are comprised by the definitions of claims 1-4 and 6-23 the search was limited to the inventive concept underlying the application and the use of the compound fully identified by name in the claims (Art. 6 PCT; Guidelines B-II, 7, last sentence, and B-III, 3.7).

Incomplete search

Claims searchable completely: 5

Claims searchable incompletely: 1-4, 6-23

Claims not searchable: -

INTERNATIONAL SEARCH REPORT

Int .onal Application No
PCT/GB 95/01995

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0558245	01-09-93	IT-B-	1254469	25-09-95
		AU-B-	660067	08-06-95
		AU-A-	3377393	26-08-93
		AU-B-	3629693	13-09-93
		BG-A-	98990	31-05-95
		CA-A-	2090156	26-08-93
		CZ-A-	9402059	15-02-95
		WO-A-	9317007	02-09-93
		FI-A-	943876	23-08-94
		JP-A-	6009606	18-01-94
		NO-A-	943140	25-08-94
		NZ-A-	245995	27-09-94
		US-A-	5403842	04-04-95
		ZA-A-	9301278	18-11-93
		CN-A-	1079738	22-12-93